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STATE-OF-THE-ART PAPER

The Pre-Clinical Animal Model in the Translational Research of Interventional Cardiology

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Scientific discoveries for improvement of human health must be translated into practical applications. Such discoveries typically begin at "the bench" with basic research, then progress to the clinical level. In particular, in the field of interventional cardiology, percutaneous cardiovascular intervention has rapidly evolved from an experimental procedure to a therapeutic clinical setting. Pre-clinical studies using animal models play a very important role in the evaluation of efficacy and safety of new medical devices before their use in human clinical studies. This review provides an overview of the emerging role, results of pre-clinical studies and development, and evaluation of animal models for percutaneous cardiovascular intervention technologies for patients with symptomatic cardiovascular disease. (J Am Coll Cardiol Intv 2009;2:373–83) © 2009 by the American College of Cardiology Foundation

The invasive/noninvasive therapies of cardiovascular disease have advanced dramatically over the last 2 decades. Such advances typically begin with basic research, then progress to the clinical level. Scientists are increasingly aware that this bench-to-bedside approach to translational research is really a 2-way street. Basic scientists provide clinicians with new tools for use in patients and for assessment of their impact, and clinical researchers make novel observations about the nature and progression of disease that often stimulate basic investigations. In particular, in the field of interventional cardiology, percutaneous cardiovascular intervention has evolved from a quirky experimental procedure to a therapeutic cornerstone for patients with symptomatic cardiovascular disease. In the development of these technologies, the role of pre-clinical testing using animal models, especially large animal models such as porcine, rabbit, and ovine, is a very important part of the regulatory process that is used to determine the safety of devices before human clinical trials. Once these technologies enter the clinical arena (bench to bedside), a further understanding of their therapeutic mechanisms can be realized through comparative analysis of animal model research findings with those of clinical pathological specimens (bedside to bench).

This review will provide an overview of the clinical application status and limitations of current percutaneous cardiovascular intervention technologies, and results of pre-clinical studies including animal models.

Experimental Animal Model for Coronary Intervention

Drug-eluting stents (DES) have driven a new era in the field of percutaneous coronary intervention (1,2). The first-generation DES coated with antiproliferative drugs have been shown to limit instent restenosis in discrete lesions (3,4). The success of these DES technologies is founded not only in initial human clinical data but also on preclinical studies using the porcine coronary restenosis model (5–8). Presently, it is unclear whether any single animal species is more predictive of the human response to such coated stents. As such, we maintain that animal models can still provide mechanistic insight into fundamental biological processes and response. Therefore, these animal models can help prove critical hypotheses regard-

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ing putative mechanisms of action of an intervention, yet they cannot be used to predict efficacy (9).

The rabbit iliac restenosis model has been studied extensively to test restenosis therapies and to understand cellular and molecular mechanisms (10–12). Although balloon angioplasty in this model does cause histopathologic injury comparable to that seen with human angioplasty, a criticism of this model is that foam cells are rare in human restenotic neointima.

The coronary arteries of domestic pigs after injury respond in a similar fashion as human coronary arteries, and thick neointima will be seen within 28 days and is identical to human restenotic neointima (Fig. 1) (13,14). In addition, the amount of neointimal thickening is directly proportional to injury, thereby permitting the creation of an injury-response regression relationship that can further quantify the response to potential treatment therapies (15,16).

Abbreviations and Acronyms

AS = aortic stenosis
CTO = chronic total occlusion
DES = drug-eluting stent(s)
LAA = left arterial appendage
MI = myocardial infarction
MR = mitral regurgitation
PES = paclitaxel-eluting stent(s)
PFO = patent foramen ovale
SES = sirolimus-eluting stent(s)
VHD = valvular heart disease

Experience suggests that the coronary arteries in domestic swine and iliac arteries of rabbits are suitable for assessment of devices that might be used in clinical evaluation (17).

Porcine coronary restenosis model for evaluation of DES technologies. Pre-clinical evaluation of novel DES technologies has great importance for understanding safety and possibly efficacy of these technologies, and the porcine coronary restenosis model is widely used for those studies. In general, cardiac catheterization techniques in the pig are similar to the techniques used in humans (18–21) (Fig. 1). A pre-clinical studies consensus group (9,22) recommends that the stent be appropriately sized by visual or quantitative coronary artery measurement using a stent/artery ratio ≤1:1, as using a higher stent/artery ratio could induce severe arterial injury and considerable coronary artery stenosis. There is no doubt that the arteries in animals cannot be fully representative of human disease, thus the pre-clinical studies can prove only safety and not true efficacy. However, pre-clinical animal studies still have predictive value because biological processes associated with arterial repair are similar. For standardization purposes, all laboratories should use similar criteria for evaluation of histopathologic change after stent implantation as follows.

INJURY AND INFLAMMATION SCORE. Inflammation by histopathologic evaluation can include an injury score at each stent strut site. Inflammation descriptions have been published previously (14,23).

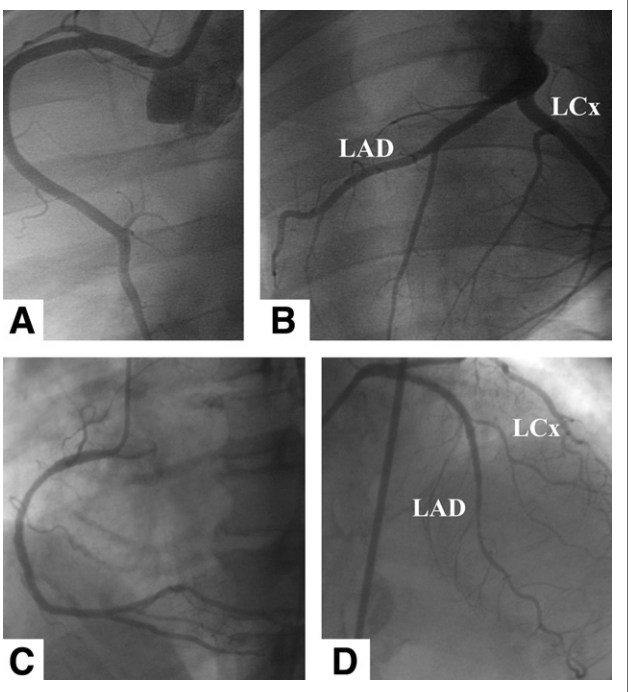

Figure 1. Porcine and Human Epicardial Coronary Anatomy

Porcine: **(A)** right coronary artery and **(B)** left coronary system. Human: **(C)** right coronary artery and **(D)** left coronary system. Similar anatomy and coronary distribution is shown of the left anterior descending (LAD), left circumflex (LCx), and right coronary arteries.

STENT STRUT POSITION AND ADJACENT TISSUE. Other observational data should include stent strut apposition to the vessel wall, stent struts covered by tissue or endothelium, adjacent tissue, including medial thinning, loss of cellularity, and hyalinization.

STENT DESIGNS. Taylor et al. (24) have studied 4 different stent designs to compare their effects on arterial injury, cellular proliferation, neointima formation, and arterial dimensions. In that study, all 4 stent designs had similar injury scores, cellular proliferation indices, and adventitial areas. Nitinol stents resulted in a 2-fold increase in neointimal area and thickness despite the lumen area being similar for all stent designs because of an offsetting expansion in vessel area in nitinol stents (20% greater than balloon-expandable stents) occurring between 7 and 14 days after stent deployment.

VASCULAR RESPONSE AND HEALING. Drug choice and release kinetics are the most important components of DES technology because they determine the type of vascular response and time course of healing (25–28). Endothelialization after stent implantation should be recorded as absent, partial, or complete in all sections and the time of re-endothelialization should be estimated. In the porcine coronary stent model, a thick neointima was reliably induced by 28 days, and several reports have investigated

the phasic, time-dependent cellular response after stenting (29–31).

SAMPLING TIME POINTS (LATE STENT THROMBOSIS IN PRECLINICAL STUDIES). Pre-clinical studies of both sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) have demonstrated their efficacy compared with that of bare-metal stents (6,8). However, enthusiasm for this technology has recently been dampened by concerns of late stent thrombosis. It was not until the results of a study using overlapping commercially available SES and PES stents in the rabbit iliac artery model showed incomplete endothelialization compared with matched bare-metal stent controls that these differences were recognized (32). Human angioscopic and autopsy data have confirmed the significant differences in healing in the clinical setting (33,34). Two studies using human autopsy samples suggested that incomplete endothelial coverage of stent struts played a very important role as the morphometric predictor of late stent thrombosis (32,34). Recently, pre-clinical data from SES, PES, and the Endeavor zotarolimus-eluting stent (Medtronic Vascular, Santa Rosa, California) have been compared (35). That study reported that incomplete endothelial coverage was seen in nonoverlapping and overlapping sites of both SES and PES compared with both zotarolimus-eluting and bare-metal stents, though the differences were more pronounced in overlapping segments (Fig. 2).

The impairment of endothelialization after DES implantation was to some extent attributed to the properties of the durable polymer and/or drug that it eluted. To accelerate the process of endothelialization and thereby reduce the risk of thrombosis and restenosis, endothelial progenitor cell-captured stents were recently developed with immobilized antibodies targeted at endothelial progenitor cell surface antigens. In in vivo porcine coronary models, a confluent monolayer of endothelial progenitor cells over and between the struts of the stent was observed at only 48 h after stent implantation and complete healing with mature neointima was observed at 28 days after stent implantation (36). The introduction of biodegradable platforms and biocompatible polymers may potentially address this issue. The pre-clinical study has investigated the absorbable metallic stent composed of magnesium alloy. Slottow et al. (37) observed the degradation of a magnesium-based absorbable metallic stent over a 3-month period in the porcine coronary model (Fig. 3).

The U.S. Food and Drug Administration has typically recommended 6-month follow-up as the interval in which to acquire pre-clinical stent data (9,22). Several time points should be used for the evaluation of DES performance, the first at 28 days to observe for neointimal hyperplasia, and at least 1 later time point to examine long-term effects. The later time point (3 or 6 months) depends on when "healing" and drug release are both complete.

OVERLAPPING STENT AND STENT FRACTURE. Stent overlap occurs often in clinical implants, and overlapping stent implantation presents the possibility of additive or synergistic effects from a drug released from the overlapped sites. Pre-clinical studies should be conducted in both single and overlap models. Stent overlap is also good for evaluating stent fracture, as it provides a hinge point for the distal stent. Stent fracture represents an undesirable mechanical failure of the prosthesis that may introduce further vessel wall injury, potentiate an inflammatory or thrombotic response, and corrupt drug delivery. Pre-clinical device studies should incorporate accepted methods to screen for acquired strut fracture (22).

OTHER CONSIDERATIONS. The advance of DES technologies mandates special consideration. In vivo dissolution chemistry, such as polymer and ceramics, should be documented by appropriately designed experiments with sufficient temporal duration beyond material degradation using histopathological methods or serial invasive/noninvasive imaging studies such as computed tomography, intravascular ultrasound, and optical coherence tomography. Another consideration relates to stents used for treatment of bifurcation and ostial lesions. Evaluation of these stent systems poses additional challenges as they often have unique shapes reflecting the peculiar anatomy they are intended to treat and/or may consist of several components. Their testing necessitates adequate anatomic models and increases the complexity of outcome analysis in the pre-clinical setting.

Porcine heat-injury restenosis model. The porcine coronary stent restenosis model is a well-accepted standard; however, the fundamental drawback of this model is that the stent itself is foreign material. As a result, this model may not be suitable to evaluate the performance of bifurcation or bioabsorbable stents due to a lack of a true stenotic lesion. Also, results of coronary artery imaging such as computed tomography, magnetic resonance imaging, intravascular ultrasound, and optical coherence tomography may be hampered as the stent can produce artifacts.

Using radiofrequency thermal balloon angioplasty, Staab et al. (38) and our laboratory (21) have investigated a porcine heat-injury restenosis model. In our study (21) using 22 swine with a total of 54 coronary arteries, coronary artery stenoses were consistently developed at 4 weeks after heat injury (Fig. 4). In light of these results, this porcine coronary restenosis model might be useful for the evaluation of bifurcation stents and bioabsorbable stents, coronary imaging studies as previously listed, and as part of the technical training for complex percutaneous coronary interventions such as bifurcation, diffuse lesion, and chronic total occlusion (21).

Animal model of vulnerable plaque. The definition of a "vulnerable" plaque varies among the literature and is

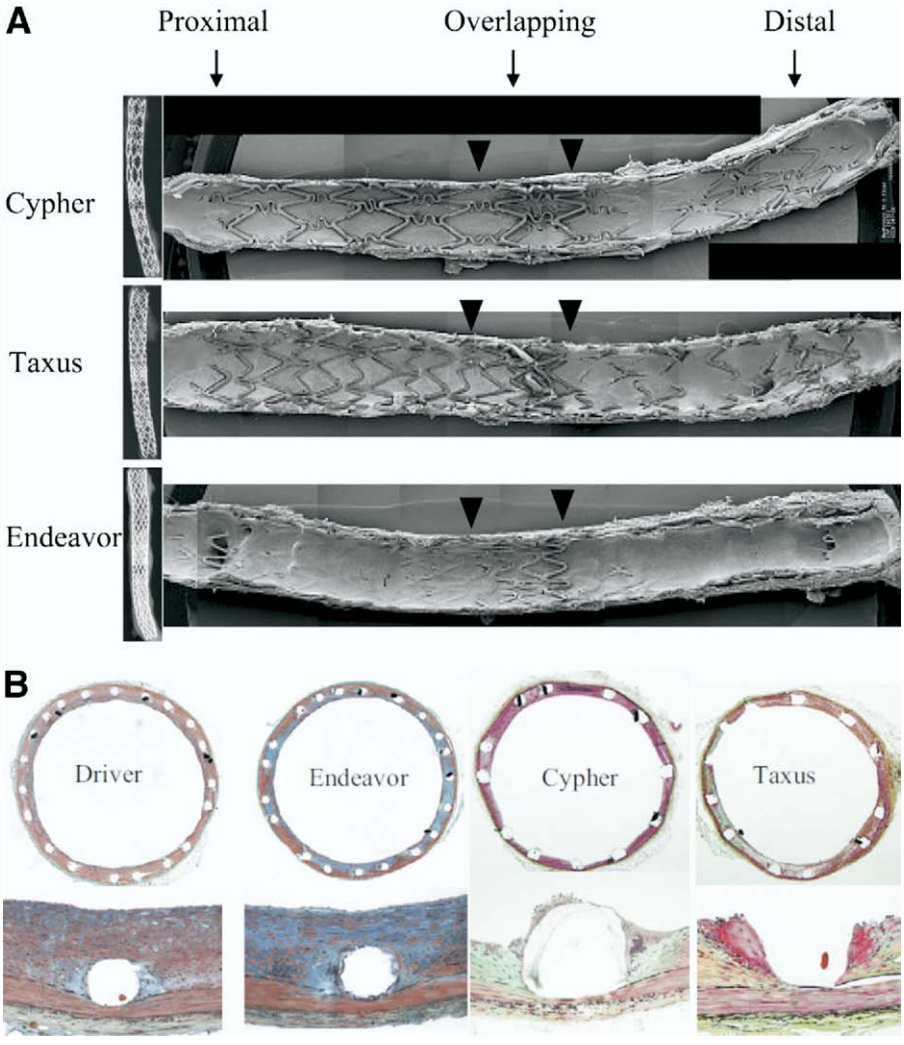

Figure 2. Comparison of Re-Endothelialization Among Drug-Eluting Stents

(A) X-rays of longitudinally cut rabbit iliac arteries at 21 days after placement of overlapping Endeavor zotarolimus-eluting stents (ZES) (Medtronic, Santa Rosa, California), Cypher sirolimus-eluting stents (SES) (Cordis Corp., Bridgewater, New Jersey), and Taxus paclitaxel-eluting stents (PES) (Boston Scientific, Natick, Massachusetts). The extent of stent coverage by endothelial cells was greatest with ZES, with almost complete coverage in the proximal and distal segments and significantly greater coverage in the overlapped segment than was found with SES and PES. **(B)** Photomicrographs showing the amount of neointimal thickness at 28 days after placement of ZES, SES, PES, and Driver bare-metal stents (Medtronic) in rabbit iliac arteries. With SES, there were focally uncovered stent struts, which were associated with inflammation consisting of heterophils or eosinophils and giant cells. Adapted, with permission, from Nakazawa et al. (35).

constantly being revised as clinicians and investigators gain more insight into the pathobiology of atherosclerosis and the conditions that lead to acute coronary syndrome and stroke (39). It is now accepted that most clinical manifestations of atherosclerosis such as acute myocardial infarction (MI), unstable angina, and sudden cardiac death result from the development of an occlusive thrombus over an underlying plaque. There are various ways in which plaques can lead to thrombus formation, the most common being plaque rupture (40). However, the mechanisms of plaque rupture and subsequent occlusive thrombus formation are still unclear. The need to identify and characterize vulnerable atherosclerotic lesions in humans has led to the development of various animal models of plaque vulnerability.

SMALL ANIMAL MODEL. Models have been developed primarily in mice, rats, and rabbits in which plaque rupture was either induced or occurred spontaneously (41–43). Recent models of plaque vulnerability continue to make use of small animals, particularly mice; however, most do not result in features of human end-stage atherosclerosis. Characteristics of human vulnerable plaque such as plaque disruption, neovascularization, intraplaque hemorrhage, and occlusive

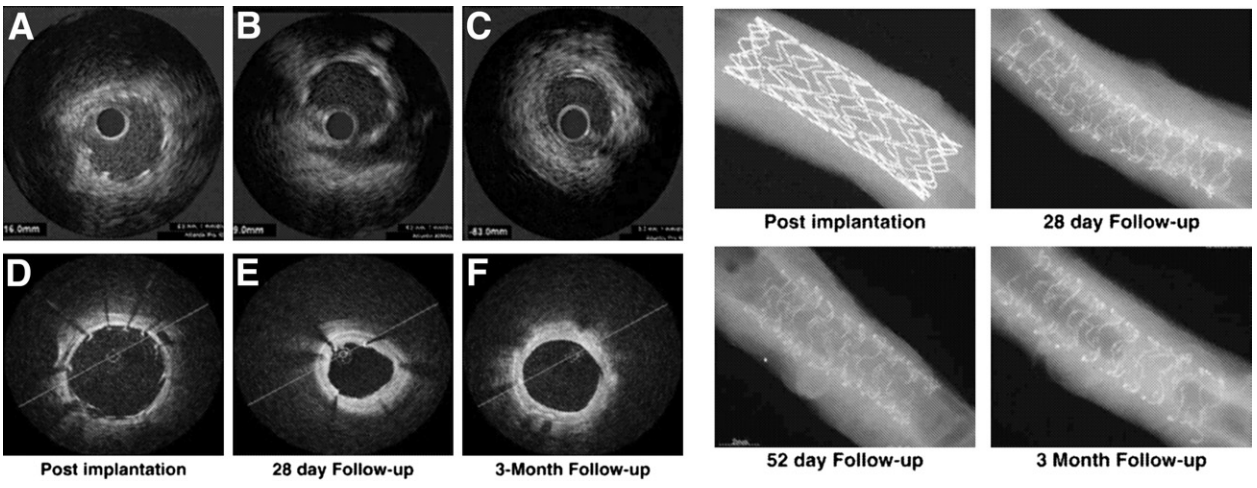

Figure 3. IVUS, OCT Images, and Radiographs of Porcine Coronary Arteries After Absorbable Metallic Stent Implantation

Intravascular ultrasound (IVUS) images: **(A)** just after implantation, **(B)** 4 weeks after implantation, **(C)** 3 months after implantation. Optical coherence tomography (OCT) images: **(D)** just after implantation, **(E)** 4 weeks after implantation, **(F)** 3 months after implantation. Adapted, with permission, from Slottow et al. (37).

thrombus formation occur rather infrequently in murine models. Also, lipoprotein metabolism in mice is largely different from that in humans, thus a murine model may not be suitable for studies examining the effects of hypolipidemic therapies on atherosclerosis or MI.

PORCINE MODEL. Granada et al. (44,45) reported that percutaneous intramural injection of cholesteryl linoleate results in the development of complex, lipid-containing inflammatory lesions in less than 4 weeks and that the intravascular ultrasound findings for the lesions in this model demonstrated similar features to those of complex human atherosclerotic plaques. However, this model is rich in smooth muscle cells/proteoglycans and the lesions lack a necrotic core, calcification, and collagen (type I) (46). Therefore, this model might be more indicative of a restenosis model.

WATANABE HERITABLE HYPERLIPIDEMIC RABBIT MODEL. Shiomi et al. (47) have developed the MI model, designated the Watanabe heritable hyperlipidemic rabbit, in which sudden cardiac events occur spontaneously without any artificial treatment. In their study, the cumulative incidence of fatal sudden cardiac events up to the age of 35 months was 97% and representative findings of MI such as vulnerable plaques as defined by Naghavi et al. (48) and thrombosis were observed in the hearts of those rabbits. This Watanabe heritable hyperlipidemic MI rabbit could be a very useful model for studying

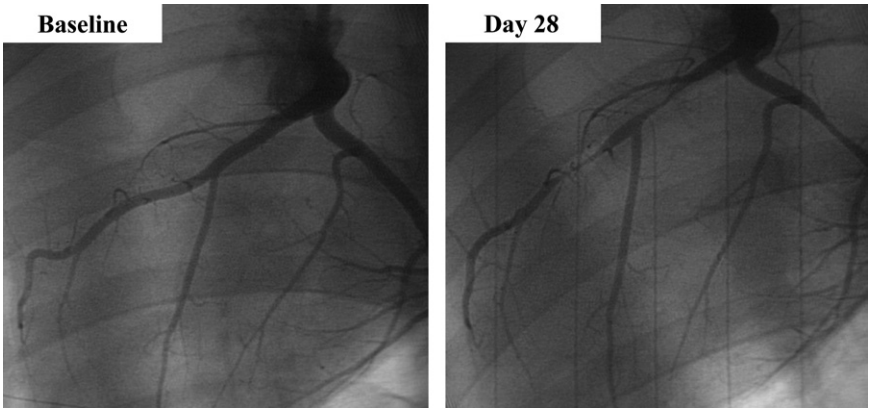

Figure 4. Representative Coronary Angiogram of the Porcine Artery Treated With Thermal Balloon

Time course of coronary artery treated with thermal balloon. A severe tandem coronary artery stenosis is observed in the left anterior descending artery at 4 weeks after thermal balloon injury. Reprinted, with permission, from Suzuki et al. (21).

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the mechanism(s) of plaque rupture and thrombogenesis and could provide a novel means for developing new therapies or imaging technologies.

Currently, there is no standard animal model for vulnerable plaque. Animal models have been invaluable in elucidating the pathobiology and complex processes of atherosclerosis, but their use in studying vulnerable plaques and end-stage atherosclerosis remains limited. We should perhaps focus our attention on unraveling the mechanisms of occlusive thrombus formation as related to plaque disruptions in humans through longitudinal imaging studies or identification of genes differentially expressed in human lesions (49).

Experimental chronic total occlusion (CTO) animal model. Recent advances of DES technologies have shifted focus within interventional cardiology to the treatment of CTO. This interest has stimulated the development of specialized devices (50,51). Despite its common occurrence, there is little information about the pathophysiology of CTO. For the past several years, researchers have developed CTO animal models to guide therapeutic investigations.

TRADITIONAL CTO ANIMAL MODEL. The initial method of producing a total occlusion used external ligature or ameroid constriction (52). However, a fundamental drawback of this method is the inability to facilitate the development of devices to recanalize CTO. Subsequent techniques for endoluminal formation of CTO in coronary and peripheral arteries have differed in their fundamental approach.

RECENT DEVELOPMENT OF CTO ANIMAL MODEL. Strauss et al. (53) subsequently modified the thrombin injection model by infusing collagenase. Several characteristics of human CTO were evident in this model, including mature fibrous tissue, multiple small intraluminal vascular channels, occasional extracellular lipid deposits, and disruption of the internal elastic lamina. Their reports (54) suggested that the microchannels may be a critical determinant of successful CTO guidewire crossing. Other CTO models have included stents with occluded outflow and even direct alcohol injection to promote thrombosis (55). Developing an accurate and reproducible humanlike coronary CTO model has been very complex because: 1) simulating luminal and medial pathology, including microcalcification, has been difficult; and 2) an inflammatory component must be present to mimic human CTO lesions (56,57). Both standard methods such as balloon angioplasty and stent implantation in animal coronary arteries rarely result in CTO development. More aggressive measures have involved the use of thermal injury and copper stent implantation as described earlier (58). Polymers have also been used to invoke chronic coronary occlusions. Early polymeric implants were abandoned as stent platforms because they induced severe inflammatory responses and vessel occlusion (59). Prosser et al. (60) reported placement of a microporous poly L-lactic acid polymer into pig and dog coronary arteries. The polymer is absorbed by 28 days, resulting in a microchanneled occlusion histologically similar to a human CTO (60). Using similar methods, Suzuki et al. and our group (61,62) have developed severe calcified CTO in pig coronary arteries (Fig. 5).

These animal models may contribute to a deeper understanding of the biology of human CTO and enable new device and pharmacological investigations to improve recanalization success in these challenging lesions.

Percutaneous Interventions for Structural Heart Disease

Recent advances of catheter-based intervention technologies have shifted focus to the treatment of structural heart disease such as valvular heart disease (VHD) and patent foramen ovale (PFO).

Percutaneous interventions for the treatment of VHD. Surgical valve repair and replacement remain controversial as sole treatments for patients with a low ejection fraction because the morbidity and mortality rates of open-heart surgery for these patients are still higher, and these reconstructive procedures have proven to be a challenge. Thus, this fact is motivating scientists to design medical devices that can treat VHD in a minimally invasive manner. Technical developments in valvular intervention culminated in the first percutaneous valve replacement in the pulmonary position, followed by replacement in the aortic position (63,64). Based on the experience gained from the development of surgical valve prostheses, the U.S. Food and Drug Administration has established guidelines for the assessment of valve implants as well as processes for in vitro and in vivo pre-clinical testing of heart valve prostheses. In these pre-clinical studies, not only device development and durability testing, but also optimal imaging and deployment protocols should be established and comprehensive user training should be initiated in the latter stages of the pre-clinical evaluation (65).

AORTIC VALVE REPLACEMENT. Degenerative aortic stenosis (AS), a common adult valvular abnormality (66), has been the focus of percutaneous treatments. Two devices are under clinical investigation for percutaneous aortic valve replacement (67,68) (Fig. 6). A committee of experts summarized that this technique is feasible and provides hemodynamic/clinical improvement for up to 2 years in patients with severe AS at high risk or with contraindications for surgery (69).

The ovine model is preferred for in vivo assessment of percutaneous aortic valve devices. Currently there is no ideal animal AS model. Even though the healthy ovine model has provided validation of catheter function, prosthesis anchoring, device function after implantation, and unimpaired

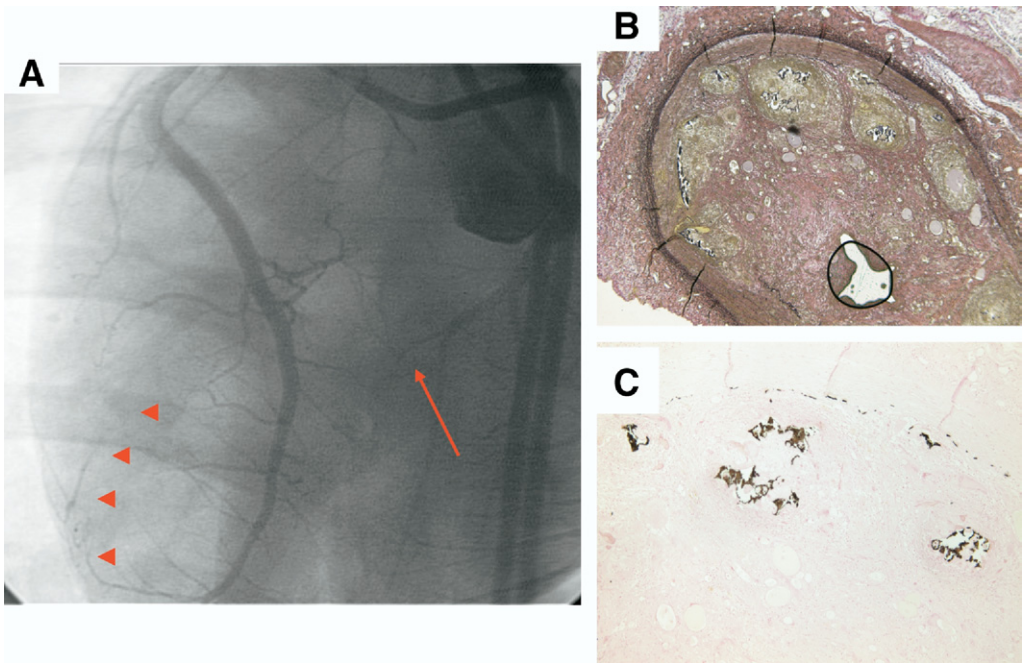

Figure 5. CTO in the Porcine Coronary Model

Angiogram at 4 weeks after implantation, demonstrating total occlusion of distal left anterior descending artery **(A)**. **Arrow** indicates the proximal site of chronic total occlusion (CTO) lesion. **Arrowheads** show the collateral arteries. Elastic Van Gieson **(B)** and Von Kossa **(C)** stained CTO segment of coronary arteries. Adapted, with permission, from Suzuki et al. (62).

coronary blood flow, this model has several limitations: 1) the size of femoral arteries (typically ≤5 mm); 2) angulation of the aortic arch (the cause of kinking of the delivery system); 3) the length of the aortic arch (shorter than that of humans); and 4) the location of coronary ostia (closer to the aortic valve than in humans).

MITRAL VALVE REPAIR. Mitral regurgitation (MR) can be caused by a myriad of pathology and pathophysiology. Primary leaflet disease, annular dilation due to dilated or ischemic cardiomyopathy, chordal abnormalities, papillary muscle dysfunction, and left ventricular dilation displacing papillary muscles can cause significant MR (70). Currently, surgical techniques using an improved understanding of the mechanisms of mitral valve dysfunction coupled with advances in catheter-based technology have resulted in several potential percutaneous approaches for mitral valve repair (71). Two approaches—edge-to-edge repair and annuloplasty—have been investigated in extensive pre-clinical testing as shown in Table 1. The first phase I feasibility trial of a percutaneous mitral device has been completed (72). The pre-clinical results have confirmed the feasibility of this approach for creation of an edge-to-edge repair (72,73). Several percutaneous technologies for mitral annuloplasty have been developed such as coronary sinus-based annuloplasty, direct intracavitary annuloplasty, and other novel cinching devices (74–78). Shortening or reshaping the annulus by insertion of a device into the coronary sinus has the potential to mimic surgical annuloplasty, and proof of this concept has been demonstrated experimentally with the recent publication of an initial human feasibility study (79).

Similar to aortic valve devices, the ovine model is preferred for in vivo assessment of percutaneous mitral valve devices. Two types of diseased animal models were mainly used (74–77). One is the rapid-pacing heart failure model and the other is the ischemic MR model. The progressive rapid ventricular pacing for 5 to 8 weeks (180 to 240 beats/min) resulted in the reduction of left ventricular ejection fraction up to 24% to 28% and moderate-to-severe MR was developed (75,76,80). One drawback of this model is that after recovery from rapid pacing, left ventricular function returns to normal levels in the healthy animals (81). Ischemic MR is induced by coronary arterial occlusion; however, variable anatomy of the coronary artery tree poses a challenge. Gorman et al. (82) has concluded that only posterior infarction by occlusion of the left circumflex could induce acute or chronic ischemic MR. Also, the primary concern of this model is the mortality and consistency of MR development. Mortality related to MI is about 30% to 40% and reliability of MR development is about 20% to 30% (82). Thus, a "diseased" model might not be necessary for device development or for durability testing of optimal deployment protocols.

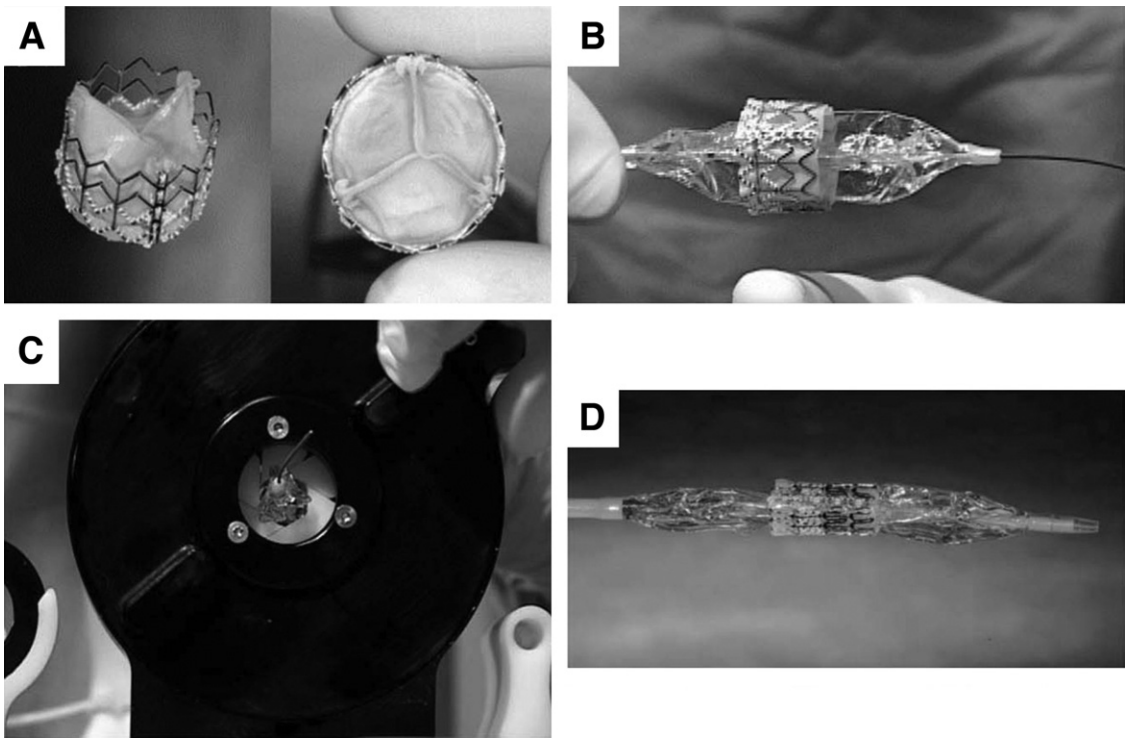

Figure 6. The Cribier-Edwards Bioprosthesis

(A) Side and upper view of the stented valve. **(B)** The bioprosthesis in position at mid-part of the balloon before crimping. **(C)** The crimping phase. **(D)** A view of the crimped valve over the balloon. Adapted, with permission, from Eltchaninoff et al. (87).

Percutaneous interventions for other structural heart disease. Stroke is the third leading cause of mortality in the developed world. Atrial fibrillation and PFO can both contribute to cardioembolic stroke. Larger left arterial appendage (LAA) size and greater LAA dysfunction have been found in patients with atrial fibrillation; therefore, amputation of the LAA at the time of mitral valve surgery has been recommended to reduce stroke risk. Recently, some groups have reported the efficacy and safety of percutaneous LAA occlusion in both pre-clinical and clinical settings (83,84). Patent foramen ovale is a congenital, flaplike opening between the atrial septa primum and secundum that persists after age 1 year.

Studies of cryptogenic stroke in young patients have shown that the incidence of PFO is higher than in patients with established causes of stroke (85). Although the optimal management of patients with symptomatic PFO remains controversial, therapeutic options for secondary stroke prevention include long-term medical treatment (platelet antiaggregating drugs or oral anticoagulation) and more invasive strategies such as surgical repair and percutaneous PFO closure. Optimal technological development will require understanding the PFO at histologic, cellular, and tissue levels. Animal models may also aid in this process (86).

Role of the Animal Model as an Educational Tool

With the advances of catheter-based intervention technologies, the indication of percutaneous catheter-based intervention has been extending and has shifted focus to the complex procedures such as multivessel disease, bifurcation lesions, unprotected left main trunk, and CTO lesions. Furthermore, new percutaneous catheter-based intervention technologies for VHDs such as AS and MR have been introduced in clinical settings (87). Although compared with the diseased human, animal models have several limitations, it should be very important for interventionalists and surgeons to learn the techniques, optimal imaging, and deployment protocols of each interventional procedure. Thus, the role of animal models should be not only in device development and durability testing, but also in physician training in optimal techniques involving new procedures.

Conclusions

The field of percutaneous cardiovascular intervention technology is evolving rapidly. The basic concepts will be important to understand as all further advances will be

Table 1. Investigations of Edge-to-Edge Repair and Annuloplasty

Repair Category/Name	Description	Status
Edge-to-edge repair		
MitraClip (Evalve)	Clip for edge-to-edge repair	Phase III clinical trial
Medtronic	Edge-to-edge repair	Pre-clinical
St. Jude	Edge-to-edge repair	Pre-clinical
Annuloplasty		
MONARCH (Edwards)	Coronary sinus-based with anchors and tensioning element	Phase I clinical trial
Carillon (Cardiac Dimensions)	Coronary sinus-based with anchors and cinching element	Phase II clinical trial
PTMA (Viacor)	Coronary sinus-based with reversible and adjustable treatment effect	Phase I clinical trial
Implant (Extensia)	Coronary sinus-based with anchors and tensioning element	Pre-clinical
Mitralign	Transventricular suture-based system using coronary sinus as anatomic guide	Phase I clinical trial
Accucinch (Guided Delivery Systems)	Transventricular annular cinching	Pre-clinical
Cordis (J&J)	Transventricular annular cinching	Pre-clinical
PS3 (Ample)	Transventricular and transseptal approach to shorten septal-lateral mitral dimension	Pre-clinical
Other		
i-Coapsys (Myocor)	Transventricular epicardial remodeling with pericardial access	Pre-clinical

generated by the early beginnings including pre-clinical studies. The experience gained with pre-clinical models permits better understanding of the important relationships between the models and the clinical results. In addition, the role of animal models should be not only in device development and durability testing, but also in training for interventionalists and surgeons in optimal techniques involving new procedures. Over the next decade, clinical trials will clarify the roles of these new approaches in relation to each other and to current surgical and medical therapies. There is a fundamental knowledge, skill set, and clinical wisdom of general physicians, imaging specialists, interventionalists, and surgeons that must be shared, coordinated, and synchronized to ensure successful outcomes and future development of the new techniques. A new era is coming yet again for the discipline of cardiovascular diseases that will be driven by the results of a collaborative relationship between the cardiologist, cardiac surgeon, and the medical device industry, benefiting the patient with symptomatic cardiovascular disease.

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REFERENCES

1. Serruys PW, Degertekin M, Tanabe K, et al., on behalf of RAVEL Study Group. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. Circulation 2002;106:798–803.
2. Sousa JE, Costa MA, Abizaid A, et al. Sirolimus-eluting stent for the treatment of in-stent restenosis: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. Circulation 2003;107:24–7.
3. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
4. Park SJ, Shim WH, Ho DS, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. N Engl J Med 2003;348:1537–45.
5. Gallo R, Padurean A, Jayaraman T, et al. Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. Circulation 1999;99:2164–70.
6. Suzuki T, Kopia G, Hayashi S, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. Circulation 2001;104:1188–93.
7. Teirstein PS. Living the dream of no restenosis. Circulation 2001;104:1996–8.
8. Heldman AW, Cheng L, Jenkins GM, et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. Circulation 2001;103:2289–95.
9. Schwartz RS, Edelman ER, Carter A, et al. Drug-eluting stents in preclinical studies: recommended evaluation from a consensus group. Circulation 2002;106:1867–73.
10. Kalinowski M, Alfke H, Bergen S, Klose KJ, Barry JJ, Wagner HJ. Comparative trial of local pharmacotherapy with L-arginine, r-hirudin, and molsidomine to reduce restenosis after balloon angioplasty of stenotic rabbit iliac arteries. Radiology 2001;219:716–23.
11. Nagae T, Aizawa K, Uchimura N, et al. Endovascular photodynamic therapy using mono-L-aspartyl-chlorin e6 to inhibit intimal hyperplasia in balloon-injured rabbit arteries. Lasers Surg Med 2001;28:381–8.
12. Kanamasa K, Otani N, Ishida N, Inoue Y, Morii H, Ishikawa K. A 7-day administration of tPA or heparin in the prevention of intimal hyperplasia following vascular injury in atherosclerotic rabbits. J Interv Cardiol 2002;15:191–5.
13. Schwartz RS, Murphy JG, Edwards WD, Camrud AR, Vliestra RE, Holmes DR. Restenosis after balloon angioplasty. A practical proliferative model in porcine coronary arteries. Circulation 1990;82:2190–200.
14. Schwartz RS, Huber KC, Murphy JG, et al. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. J Am Coll Cardiol 1992;19:267–74.
15. Schwartz RS, Holder DJ, Holmes DR, et al. Neointimal thickening after severe coronary artery injury is limited by a short-term administration of a factor Xa inhibitor. Results in a porcine model. Circulation 1996;93:1542–8.
16. Huber KC, Schwartz RS, Edwards WD, et al. Effects of angiotensin converting enzyme inhibition on neointimal proliferation in a porcine coronary injury model. Am Heart J 1993;125:695–701.
17. Schwartz RS, Edelman ER, Carter A, et al. Preclinical evaluation of drug-eluting stents for peripheral applications: recommendations from an expert consensus group. Circulation 2004;110:2498–505.
18. Ikeno F, Buchbinder M, Yeung AC. Novel stent and delivery systems for the treatment of bifurcation lesions: porcine coronary artery model. Cardiovasc Revasc Med 2007;8:38–42.

19. Ikeno F, Inagaki K, Rezaee M, Mochly-Rosen D. Impaired perfusion after myocardial infarction is due to reperfusion-induced deltaPKC-mediated myocardial damage. Cardiovasc Res 2007;73:699–709.
20. Suzuki Y, Lyons JK, Yeung AC, Ikeno F. In vivo porcine model of reperfused myocardial infarction: in situ double staining to measure precise infarct area/area at risk. Catheter Cardiovasc Interv 2008;71:100–7.
21. Suzuki Y, Lyons JK, Yeung AC, Ikeno F. The porcine restenosis model using thermal balloon injury: comparison with the model by coronary stenting. J Invasive Cardiol 2008;20:142–6.
22. Schwartz RS, Edelman ER, Virmani R, et al. Drug-eluting stents in preclinical studies; updated consensus recommendations for preclinical evaluation. Circulation Cardiovasc Interv 2008;1:143–53.
23. Kornowski R, Hong MK, Tio FO, Bramwell O, Wu H, Leon MB. In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia. J Am Coll Cardiol 1998;31:224–30.
24. Taylor AJ, Gorman PD, Kenwood B, Hudak C, Tashko G, Virmani R. A comparison of four stent designs on arterial injury, cellular proliferation, neointima formation, and arterial dimensions in an experimental porcine model. Catheter Cardiovasc Interv 2001;53:420–5.
25. Tanner FC, Boehm M, Akyurek LM, et al. Differential effects of the cyclin-dependent kinase inhibitors p27(Kip1), p21(Cip1), and p16(Ink4) on vascular smooth muscle cell proliferation. Circulation 2000;101:2022–5.
26. Sun J, Marx SO, Chen HJ, Poon M, Marks AR, Rabbani LE. Role for p27(Kip1) in vascular smooth muscle cell migration. Circulation 2001;103:2967–72.
27. Vinals F, Chambard JC, Pouyssegur J. p70 S6 kinase-mediated protein synthesis is a critical step for vascular endothelial cell proliferation. J Biol Chem 1999;274:26776–82.
28. Abal M, Andreu JM, Barasoain I. Taxanes: microtubule and centrosome targets, and cell cycle dependent mechanisms of action. Curr Cancer Drug Targets 2003;3:193–203.
29. Carter AJ, Laird JR, Farb A, Kufs W, Wortham DC, Virmani R. Morphologic characteristics of lesion formation and time course of smooth muscle cell proliferation in a porcine proliferative restenosis model. J Am Coll Cardiol 1994;24:1398–405.
30. Edelman ER, Rogers C. Pathobiologic responses to stenting. Am J Cardiol 1998;81:4E–6E.
31. Virmani R, Kolodgie FD, Farb A, Lafont A. Drug eluting stents: are human and animal studies comparable? Heart 2003;89:133–8.
32. Finn AV, Kolodgie FD, Harnek J, et al. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. Circulation 2005;112:270–8.
33. Kotani J, Awata M, Nanto S, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. J Am Coll Cardiol 2006;47:2108–11.
34. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.
35. Nakazawa G, Finn AV, John MC, Kolodgie FD, Virmani R. The significance of preclinical evaluation of sirolimus-, paclitaxel-, and zotarolimus-eluting stents. Am J Cardiol 2007;100:36M–44M.
36. OrbusNeich. Genous [online images]. Available at: http://www.orbusneich.com/genous/invivo/animation/?PHPSESSID=6ad47ba6db4b3d91788bd72420b070fc. Accessed April 12, 2009.
37. Slottow TL, Pakala R, Okabe T, et al. Optical coherence tomography and intravascular ultrasound imaging of bioabsorbable magnesium stent degradation in porcine coronary arteries. Cardiovasc Revasc Med 2008;9:248–54.
38. Staab ME, Srivatsa SS, Lerman A, et al. Arterial remodeling after experimental percutaneous injury is highly dependent on adventitial injury and histopathology. Int J Cardiol 1997;58:31–40.
39. Schapira K, Heeneman S, Daemen MJ. Animal models to study plaque vulnerability. Curr Pharm Des 2007;13:1013–20.
40. Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. J Am Coll Cardiol 2005;46:937–54.
41. Nakamura M, Abe S, Kinukawa N. Aortic medial necrosis with or without thrombosis in rabbits treated with Russell's viper venom and angiotensin II. Atherosclerosis 1997;128:149–56.
42. Eitzman DT, Westrick RJ, Xu Z, Tyson J, Ginsburg D. Hyperlipidemia promotes thrombosis after injury to atherosclerotic vessels in apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol 2000;20:1831–4.
43. von der Thusen JH, van Vlijmen BJ, Hoeben RC, et al. Induction of atherosclerotic plaque rupture in apolipoprotein E−/− mice after adenovirus-mediated transfer of p53. Circulation 2002;105:2064–70.
44. Granada JF, Moreno PR, Burke AP, Schulz DG, Raizner AE, Kaluza GL. Endovascular needle injection of cholesteryl linoleate into the arterial wall produces complex vascular lesions identifiable by intravascular ultrasound: early development in a porcine model of vulnerable plaque. Coron Artery Dis 2005;16:217–24.
45. Granada JF, Wallace-Bradley D, Win HK, et al. In vivo plaque characterization using intravascular ultrasound-virtual histology in a porcine model of complex coronary lesions. Arterioscler Thromb Vasc Biol 2007;27:387–93.
46. Virmani R, Nakazawa G. Animal models and virtual histology. Arterioscler Thromb Vasc Biol 2007;27:1666, author reply 1667–8.
47. Shiomi M, Ito T, Yamada S, Kawashima S, Fan J. Correlation of vulnerable coronary plaques to sudden cardiac events. Lessons from a myocardial infarction-prone animal model (the WHHLMI rabbit). J Atheroscler Thromb 2004;11:184–9.
48. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part I. Circulation 2003;108:1664–72.
49. Faber BC, Cleutjens KB, Niessen RL, et al. Identification of genes potentially involved in rupture of human atherosclerotic plaques. Circ Res 2001;89:547–54.
50. Ng W, Chen W-H, Lee P-Y, Lau C-P. Initial experience and safety in the treatment of chronic total coronary occlusions with a new optical coherent reflectometry-guided radiofrequency ablation guidewire. Am J Cardiol 2003;92:732–4.
51. Orlic D, Stankovic G, Sangiorgi G, et al. Preliminary experience with the Frontrunner coronary catheter: novel device dedicated to mechanical revascularization of chronic total occlusions. Catheter Cardiovasc Interv 2005;64:146.
52. Elzinga WE. Ameroid constrictor: uniform closure rates and a calibration procedure. J Appl Physiol 1969;27:419–21.
53. Strauss BH, Goldman L, Qiang B, et al. Collagenase plaque digestion for facilitating guide wire crossing in chronic total occlusions. Circulation 2003;108:1259–62.
54. Strauss BH, Segev A, Wright GA, et al. Microvessels in chronic total occlusions: pathways for successful guidewire crossing? J Interv Cardiol 2005;18:425–36.
55. Nikol S, Armeanu S, Engelmann MG, et al. Evaluation of endovascular techniques for creating a porcine femoral artery occlusion model. J Endovasc Ther 2001;8:401–7.
56. Katsuragawa M, Fujiwara H, Miyamae M, Sasayama S. Histologic studies in percutaneous transluminal coronary angioplasty for chronic total occlusion: comparison of tapering and abrupt types of occlusion and short and long occluded segments. J Am Coll Cardiol 1993;21:604–11.
57. Srivatsa SS, Edwards WD, Boos CM, et al. Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. J Am Coll Cardiol 1997;29:955–63.
58. Suzuki Y, Lyons JK, Yeung AC, Ikeno F. The porcine restenosis model using thermal balloon injury: comparison with the model by coronary stenting. J Invasive Cardiol 2008;20:142–6.
59. Tanguay JF, Zidar JP, Phillips HR, Stack RS. Current status of biodegradable stents. Cardiol Clin 1994;12:699–713.
60. Prosser L, Agrawal CM, Polan J, Elliott J, Adams DG, Bailey SR. Implantation of oxygen enhanced, three-dimensional microporous L-PLA polymers: a reproducible porcine model of chronic total coronary occlusion. Catheter Cardiovasc Interv 2006;67:412–6.
61. Suzuki K, Saito N, Zhang G, et al. Development of a novel calcified total occlusion model in porcine coronary arteries. J Invasive Cardiol 2008;20:296–301.

62. Suzuki Y, Oyane A, Ikeno F, Lyons JK, Yeung AC. Development of animal model for calcified chronic total occlusion (cto). Catheter Cardiovasc Interv 2009 Feb 2 [E-pub ahead of print].
63. Bonhoeffer P, Boudjemline Y, Saliba Z, et al. Transcatheter implantation of a bovine valve in pulmonary position: a lamb study. Circulation 2000;102:813–6.
64. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006–8.
65. Fann JI, Chronos N, Rowe SJ, et al. Evolving strategies for the treatment of valvular heart disease: preclinical and clinical pathways for percutaneous aortic valve replacement. Catheter Cardiovasc Interv 2008;71:434–40.
66. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231–43.
67. Cribier A, Eltchaninoff H, Tron C, et al. Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis. J Am Coll Cardiol 2004;43:698–703.
68. Grube E, Laborde JC, Gerckens U, et al. Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: the Siegburg first-in-man study. Circulation 2006;114:1616–24.
69. Vahanian A, Alfieri O, Al-Attar N, et al., on behalf of European Association of Cardio-Thoracic Surgery, European Society of Cardiology, European Association of Percutaneous Cardiovascular Interventions. Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2008;29:1463–70.
70. Otto CM. Clinical practice. Evaluation and management of chronic mitral regurgitation. N Engl J Med 2001;345:740–6.
71. Gillinov AM, Liddicoat JR. Percutaneous mitral valve repair. Semin Thorac Cardiovasc Surg 2006;18:115–21.
72. Feldman T, Wasserman HS, Herrmann HC, et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. J Am Coll Cardiol 2005;46:2134–40.
73. Alfieri O, Elefteriades JA, Chapolini RJ, et al. Novel suture device for beating-heart mitral leaflet approximation. Ann Thorac Surg 2002;74:1488–93.
74. Liddicoat JR, Mac Neill BD, Gillinov AM, et al. Percutaneous mitral valve repair: a feasibility study in an ovine model of acute ischemic mitral regurgitation. Catheter Cardiovasc Interv 2003;60:410–6.
75. Kaye DM, Byrne M, Alferness C, Power J. Feasibility and short-term efficacy of percutaneous mitral annular reduction for the therapy of heart failure-induced mitral regurgitation. Circulation 2003;108:1795–7.
76. Maniu CV, Patel JB, Reuter DG, et al. Acute and chronic reduction of functional mitral regurgitation in experimental heart failure by percutaneous mitral annuloplasty. J Am Coll Cardiol 2004;44:1652–61.
77. Daimon M, Shiota T, Gillinov AM, et al. Percutaneous mitral valve repair for chronic ischemic mitral regurgitation: a real-time three-dimensional echocardiographic study in an ovine model. Circulation 2005;111:2183–9.
78. Feldman T. Percutaneous valve repair and replacement: challenges encountered, challenges met, challenges ahead. Circulation 2006;113:771–3.
79. Webb JG, Harnek J, Munt BI, et al. Percutaneous transvenous mitral annuloplasty: initial human experience with device implantation in the coronary sinus. Circulation 2006;113:851–5.
80. Komamura K, Shannon RP, Pasipoularides A, et al. Alterations in left ventricular diastolic function in conscious dogs with pacing-induced heart failure. J Clin Invest 1992;89:1825–38.
81. Yamamoto K, Burnett JC Jr., Meyer LM, Sinclair L, Stevens TL, Redfield MM. Ventricular remodeling during development and recovery from modified tachycardia-induced cardiomyopathy model. Am J Physiol 1996;271:R1529–34.
82. Gorman RC, McCaughan JS, Ratcliffe MB, et al. Pathogenesis of acute ischemic mitral regurgitation in three dimensions. J Thorac Cardiovasc Surg 1995;109:684–93.
83. Nakai T, Lesh MD, Gerstenfeld EP, Virmani R, Jones R, Lee RJ. Percutaneous left atrial appendage occlusion (PLAATO) for preventing cardioembolism: first experience in canine model. Circulation 2002;105:2217–22.
84. Chiam PT, Ruiz CE. Percutaneous transcatheter left atrial appendage exclusion in atrial fibrillation. J Invasive Cardiol 2008;20:E109–13.
85. Schwerzmann M, Windecker S, Wahl A, et al. Percutaneous closure of patent foramen ovale: impact of device design on safety and efficacy. Heart 2004;90:186–90.
86. Hara H, Virmani R, Ladich E, et al. Patent foramen ovale: standards for a preclinical model of prevalence, structure, and histopathologic comparability to human hearts. Catheter Cardiovasc Interv 2007;69:266–73.
87. Eltchaninoff H, Zajarias A, Tron C, et al. Transcatheter aortic valve implantation: technical aspects, results and indications. Arch Cardiovasc Dis 2008;101:126–32.

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